Drug safety during pregnancy: can we analyze teratogenic drug prescriptions?

Ferdinand Dhombres, Kin Wah Fung, Laritza M. Rodriguez, Olivier Bodenreider

Lister Hill National Center for Biomedical Communications, National Library of Medicine
National Institutes of Health, 8600 Rockville Pike, Bethesda MD 20894, USA
ferdinand.dhombres@nih.gov, kwfung@nlm.nih.gov, laritza.rodriguez@nih.gov, olivier.bodenreider@nih.gov

Abstract

Objectives*: To assess the extent to which teratogenic drugs are prescribed during pregnancy and to investigate. the feasibility of an alert system at the point of prescription, in order to improve drug safety during pregnancy.* ***Methods****: We establish a reference list of teratogenic drugs by merging lists of teratogenic drugs published in the literature, extract drug prescriptions to pregnant women from a clinical dataset, and compare the drugs prescribed to pregnant women to the reference list of teratogenic drugs. Finally, we compare the results across drug categories (FDA, FASS and ADEC) and mechanisms of action and count how many alerts would be generated with each reference.* ***Results****: A total of 9915 prescriptions of systemic teratogenic drug during pregnancy was identified in our dataset among the 68,699 items prescribed to 89,735 pregnant women. The agreement among sources is limited. The number of potential alerts generated based on FDA, FASS, ADEC is 305, 337 and 1438, respectively. Based on the mechanism of action, 8880 alerts would be generated.* ***Conclusions****: It is possible to analyze teratogenic drug prescriptions in a clinical dataset in reference to FDA, FASS and ADEC categories. But the current sources of teratogenicity information cannot effectively support drug safety.*

Keywords:

drug safety, teratogenic agents, pregnancy, clinical data, clinical decision support

Introduction

In the past three decades, there has been a progressive, but significant increase in the use of drug during pregnancy [1, 2]. Precise information about the adverse effects of drugs on fetal development is sparse and scattered. A drug can cause congenital malformations when the exposure occurs at a specific time in pregnancy and at a given dose. The definition of teratogenic exposure includes the teratogenic agent (the drug), the dose and the time in pregnancy [3]. For example, in utero exposure to *thalidomide* (widely used in the 1960s) at an early stage of pregnancy induces limb reduction defects [4]. Analogously, the use of *valproic acid* in early pregnancy is associated with a dose-dependent risk of major congenital malformations [5]. In this paper, the term "teratogenic drug" refers to a teratogenic agent.

The evaluation of the actual cause of a malformation in the context of exposure to a teratogenic agent can be assessed based on epidemiologic studies and animal developmental toxicity studies. Of particular importance are dose-effect studies and studies that help establish biological plausibility (e.g., by analyzing the mechanism of action of the drug and the nature of the malformation in light of known teratology principles) [3].

In this paper we review two knowledge bases about drug teratogenicity and analyze a clinical dataset for evidence of prescription of such drugs to pregnant women. Our main objective is to assess the extent to which teratogenic drugs are prescribed during pregnancy. This work also investigates the feasibility of an alert system at the point of prescription, in order to improve drug safety during pregnancy.

Background

In this section, we review related work on teratogenic drugs and clinical decision support for drug safety, and introduce some of the drug terminologies and classification systems used in our investigation, including ATC, NDC and RxNorm.

Related work

Knowledge about teratogenic drugs. Publications about teratogenic dugs generally focus on a specific drug (or small set of drugs) and aim to provide precise information about teratology of a specific drug (e.g. [5, 6]). Other publications are expert reviews gathering information about these drugs and providing lists of teratogenic agents [3, 7, 8]. Fewer publications are population-based, providing exposure studies associated with pediatric outcomes [9-11].

Teratogenic mechanisms for drugs have been analyzed by van Gelder *et al.* based on an extensive literature review, along with a list of the corresponding drugs and drug classes [7]. This reference list was used to analyze potentially teratogenic drugs dispensed to pregnant women in the Netherlands [9]. Along the same lines, another list of drugs was established by Zomerdijk *et al.* based on recommendations from (i) the U.S. Food and Drug Administration (FDA), (ii) the Australian Drug Evaluation Committee (ADEC) and (iii) the Swedish Catalogue of Approved Drugs (FASS) [11]. Drugs are classified according to the risk of toxicity during pregnancy and the potential benefits for the use of the drug. In this paper, drugs are considered teratogenic when there is documented fetal risk in humans. This definition includes the following categories: FDA category D and X; ADEC category D and X; and FASS category D. The FDA, ADEC and FASS classifications provide a list of teratogenic drugs, along with a comprehensive description of the teratogenicity risk for each drug. Here, we summarize the relevant categories as defined in [11]:

- **ADEC category D**: "Drugs which have caused are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage."
- **ADEC category X**: "Drugs which have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy."
- **FDA category C**: "Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risk."
- **FDA category D**: "There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks."
- **FDA category X**: "Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks of the use of the drug in pregnant women clearly outweighs any possible benefit."
- **FASS category B3**: "Medicinal products which may be assumed to have been used by only a limited number of pregnant women and women of child-bearing age, without any identified disturbance in the reproductive process having been noted so far, e.g. an increased incidence of malformations or other direct or indirect harmful effect on the fetus. Reproduction toxicity studies in animals have revealed an increased incidence of fetal damage or other deleterious effects on the reproductive process, the significance of which is considered uncertain in man."
- **FASS category C**: "Medicinal products which by their pharmacological effects have caused, or must be suspected of causing, disturbances in the reproductive process that may involve risk to the fetus without being directly teratogenic. If experimental studies in animals have indicated an increased occurrence of fetal injuries or other injurious effects on the reproductive process of uncertain significance in humans, these findings are to be stated in this category."
- **FASS category D**: "Medicinal products which have caused an increased incidence of fetal malformations or other permanent damage in man or which, on the basis of e.g. reproduction toxicity studies, must be suspected of doing so. This category comprises drugs with primary teratogenic effects. If the product also has pharmacological effects that may directly or indirectly have a harmful effect on the fetus, this must also be stated."

For example, *phenobarbital* is a category D drug for the FDA classification and for the FASS classification.

Of note, until December 2014, the FDA required drug manufactures to include the Pregnancy Risk category in all the Structured Product Labels (SPL). The Code of Federal Regulations Title 21 changed the requirements for Section 8.1 of the SPL to: ‘This subsection may be omitted only if the drug is not absorbed systemically and the drug is not known to have a potential for indirect harm to the fetus.’ [12] The required inclusion of a Pregnancy Risk Category in all systemic drugs aims to improve awareness of potential teratogenic effects to the embryo and fetus. However, recent studies demonstrate that the information is missing in approximately 20% of the FDA labels [13].

Clinical decision support for drug safety. A clinical support system for drug alerts in pregnant women would be useful to health care providers in charge of prenatal care. It has been estimated that on a daily basis there are at least one million pregnant women in the USA, many of which do not have access to specialized care namely obstetricians. A system that could alert primary care providers and even the patients themselves about the risks of use of drugs during the different trimesters of pregnancy would be most useful. The use of Computerized Physician Order Entry (CPOE) has been shown to reduce prescription error rates [14]. Similar result can be expected in the specific context of pregnancy. However, a precise analysis of the alerts generated is required to effectively support drug safety [15].

Drug terminologies and classification systems

ATC is used as a reference terminology for teratogenic drugs and drug classes. Our prescription dataset identifies drugs with codes from the NDC system and we use RxNorm for information about dose forms.

Anatomical Therapeutic Classification (ATC). The Anatomical Therapeutic Chemical (ATC) drug classification is maintained by the World Health Organization [16]. ATC is a reference for pharmacoepidemiology. The system classifies drugs at five levels. The fifth level corresponds to drugs or ingredients, while the other levels correspond to drug classes, namely 1) anatomical, 2) therapeutic, 3) pharmacological, and 4) chemical. For example the ATC drug “CAPROPRIL” (C09AA01, level 5) is classified under “ACE inhibitors, plain” (C09AA, level 4), “ACE INHIBITORS, PLAIN” (C09A, level 3), “AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM” (C09, level 2) and “CARDIOVASCULAR SYSTEM” (C, level 1). Knowledge bases about drug teratogenicity often refer to ATC for identifying drugs and drug classes.

National Drug Code (NDC). In many prescription datasets, drug products are identified with a unique number, called the National Drug Code (NDC). All prescription drugs currently on the U.S. market have an NDC. In addition to the drug product, the NDC also contains manufacturer and packaging information. However, information about the drug, its strength and dose form are not directly or explicitly represented in the NDC and must be extracted from other drug information sources to which NDCs are linked, e.g., RxNorm.

RxNorm. RxNorm is a standardized nomenclature for clinical drugs integrating 15 drug source terminologies, and maintained by the National Library of Medicine (NLM) [17]. As mentioned above, NDCs are integrated in RxNorm. RxNorm provides dose form information for each clinical drug a dose form (e.g., pill, injectable solution, cream), making it possible to distinguish between topical (e.g., cream) and systemic drugs (e.g., pill). For example, the NDC 00049342041 corresponds to the RxNorm entity Fluconazole 100 MG Oral Tablet (197698), whose dose form group is Pill.

Materials and Methods

Our approach to identifying teratogenic drug prescriptions can be summarized as follows. We establish a reference list of teratogenic drugs by merging lists of teratogenic drugs published in the literature; we extract drug prescriptions to pregnant women from a clinical dataset; we compare the drugs prescribed to pregnant women to the reference list of teratogenic drugs. Finally, we compare the results across drug categories and mechanisms of action. We apply this method to a large clinical dataset covering 5.3M patients, 26.5K drugs and 1.9M prescription items.

Clinical dataset

Our clinical dataset was acquired from Symphony Health Solutions (http://symphonyhealth.com/). It includes one year of prescription data from the Washington, D.C. core based statistical area (i.e., Washington, D.C., West

Virginia, and several counties in Maryland and Virginia) in the United States[1], from July 1, 2011 through June 30, 2012. The sources of data come from major supply channels (retail pharmacies, wholesalers, specialty pharmacies, hospitals, clinical registries, electronic medical records, health plan claims, and government program claims).
Prescription information includes prescriber, de-identified patient information, and specific medication information, such as the National Drug Code (NDC), the generic drug name, strength, date dispensed, and quantity. The database also includes billing data, specifically CPT and ICD-9-CM codes, for inpatient hospitalizations, emergency room visits, and outpatient visits in the same geographic area over the same time period. More specifically, the diagnoses are coded with the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and the procedures are coded with the Current Procedural Terminology (CPT). The dataset does not include any clinical findings, such as laboratory or radiology results, progress notes, or physical exam findings, other than what can be inferred from diagnosis codes.

The total population in the dataset is 5.4M with 57% of women and a total of 1.9M prescription items. More details about the population represented in the dataset can be found in Table 1.

	n	(%)
Total population	5,383,678	
Women	3,088,881	(57.4%)
Total patient with a least one prescription	1,942,038	
Female patients with a least one prescription	1,114,408	(57.4%)

Table 1. The population of the Symphony dataset (time period from July 1, 2011 through June 30, 2012.)

Establishing a reference list of teratogenic drugs. We chose two recent articles providing different lists of teratogenic drugs, based on different points of view. Both articles provides a list of drugs with the corresponding ATC codes validated in a clinical setting. More specifically, one article, [9], provides a list of ATC codes at different levels of granularity, from individual drugs (ATC level 5) to drug classes (ATC levels 2 to 4). In the other article, [11], all the drugs are listed as individual drugs (level 5), along with their categories in the FDA, FASS and ADEC teratogenicity classifications.

We merged the drugs from the two articles based on ATC level 5 drugs after expanding drug classes (levels 2 to 4) into their individual members (level 5). We obtained two groups of teratogenic drugs: one is organized by the FDA, FASS and ADEC categories and the other is organized by mechanism of action of the drug.
For example, the drug CAPTOPRIL is categorized "D" in all three classifications and its mechanism of action is "ACE inhibitors/AT II receptor antagonists".

Extracting drug prescriptions to pregnant women. In order to establish a list of drug prescriptions in pregnant women from our dataset, we have to (i) identify pregnant women in the population; (ii) restrict prescriptions to systemic drugs; and (iii) select the prescriptions occurring during pregnancy.

Identifying pregnant women. We identify pregnant women based on diagnoses and procedures that denote (or at least are consistent with) ongoing pregnancy, excluding the early stages of pregnancy (i.e., before pregnancy has been confirmed) and late stages (i.e., after delivery might have occurred). One author (FD) searched ICD-9-CM and CPT for terms containing "fetus", "pregnancy", "antepartum", "ultrasound", "labor" or "delivery" and reviewed all the corresponding codes and hierarchies to select codes of interest. In ICD-9-CM, we exclude codes related to labor, delivery and ectopic pregnancy; in CPT, we exclude labor, delivery and abortion procedures.

Examples of codes indicative of pregnancy include "Anemia of mother, antepartum condition or complication" (64823) in ICD-9-CM and "Doppler velocimetry, fetal; umbilical artery" (76820) in CPT.

Restricting prescriptions to systemic drugs. Topical drugs have a limited systemic uptake after local administration and are therefore associated with a reduced potential to cause birth defects [18]. Therefore, we limited our analysis to systemic drugs. Drug identifiers in the clinical dataset (NDCs) were mapped to RxNorm using the RxNorm API (https://rxnav.nlm.nih.gov/RxNormAPIs.html). Leveraging RxNorm, we used the dose form group information provided for each drug to select systemic drugs. More specifically, we restricted prescriptions to drugs to oral solid dose forms (Pill) and other dose form groups for systemic drugs, including

[1] Detailed information on core based statistical area is available on the United State Census Bureau website , at http://www.census.gov/population/metro/data/def.html

Injectable solution, Transdermal Patch and Inhalant product. For example, the NDC 00143117201 corresponds to CAPTOPRIL 25MG in tablets, the corresponding RxCui is 1998 and the Dose Form Group is "Pill".

Selecting the prescriptions occurring during pregnancy. Since our objective is to assess the extent to which certain drugs are prescribed to pregnant women (i.e., during pregnancy), we need to exclude prescriptions made to women before the beginning of the pregnancy or after delivery has occurred. The codes selected for diagnoses and procedures denote pregnancy at the date the diagnosis was made or the procedure was performed. Because most of these codes correspond to diagnoses and procedures associated with the second trimester of pregnancy, we take a window of 90 days prior, knowing that it will not cover the entire pregnancy, but will unlikely cover a period not corresponding to pregnancy. We consider all prescriptions occurring in this period.

Identifying prescriptions of teratogenic drugs occurring during pregnancy

Having established a reference list of teratogenic drugs and identified drug prescriptions to pregnant women, we identify prescriptions of teratogenic drugs occurring during pregnancy by searching the names of teratogenic drugs from the reference (identified in reference to ATC) in the prescription data of our clinical dataset (generic names), restricted to prescriptions of systemic drugs to pregnant women. We analyze the prescriptions with respect to mechanism of action and to teratogenicity category according to the various sources (FDA, FASS, and ADEC).

Comparison among sources of teratogenicity information for generating alerts

For each teratogenic drug, we compare the category assigned to the drug by the three sources of teratogenicity information, namely FDA, FASS, and ADEC, and contrast it with teratogenicity information based on the mechanism of action. We also count how many alerts would be generated by a CPOE system if each source was used as the basis for identifying teratogenic drugs.

Results

Establishing a reference list of teratogenic drugs

The list of drugs and drug classes derived from paper [9] contains a total 701 teratogenic drugs and 11 mechanisms of action. One drug can be associated with more than one mechanism of action. The list of drugs derived from paper [11] contains 210 teratogenic drugs, among all the corresponding categories in FDA, FASS and ADEC classifications.

Extracting drug prescriptions to pregnant women

We identified 196 diagnosis codes from ICD-9-CM and 39 procedure codes from CPT, which are indicative of or consistent with an ongoing pregnancy. The total number of pregnant women identified in our dataset is 89,735 (see Table 2). We found a total of 68,699 items prescribed to pregnant women.

	n	**(%)**
Female population	3,088,881	
Pregnant women	89,735	(2.9%)
Female patients with a least one prescription	1,114,408	
Female patients with a least one prescription during pregnancy	15,851	(1.4%)
Female patients with a least one prescription of a teratogenic drug during pregnancy	5,837	(0.5%)
Number of drug prescriptions during pregnancy	68,699	
Number of teratogenic drug prescriptions during pregnancy	9,915	(14.4%)

Table 2. Prescriptions in pregnant women in the Symphony dataset
(time period from July 1, 2011 through June 30, 2012.)

Identifying prescriptions of teratogenic drugs occurring during pregnancy

A total of 9915 prescriptions of systemic teratogenic drug during pregnancy were identified in our dataset (Table 2). The frequency of these prescriptions organized by specific categories of drug in pregnancy (FDA category D and X, ADEC category D and X, FASS category D) and by mechanism of action is presented in Table 3 and Table 4, respectively.

Classification	# of prescriptions
FDA	
C	1119
D	120
X	185
FASS	
B3	1052
C	18
D	337
ADEC	
D	1276
X	162

Table 3. Frequency of prescription by classes of teratogenic drugs

Mechanism of action	# of prescriptions
Vascular disruption (e.g., IBUPROFEN, NAPROXEN)	5152
COX inhibitors (e.g., CELECOXIB)	3753
Oxidative stress (e.g., NIFEDIPINE, METRONIDAZOLE)	3323
Serotonin signalling disturbance (e.g., ONDANSETRON)	1030
GABA receptor antagonists (e.g., ALPRAZOLAM)	546
Folate antagonism (e.g., LAMOTRIGINE)	131
ACE inhibitors/AT II receptor antagonists (e.g., OLMESARTAN)	110
Endocrine disruption (e.g., ESTRADIOL)	72
Carbonic anhydrase inhibition (e.g., TOPIRAMATE)	44
HMG-CoA reductase inhibitors (e.g., SIMVASTATIN)	23
Neural crest cell disruption (e.g., KETOCONAZOLE)	3

Table 4. Frequency of prescription by mechanism of action

Comparison among sources of teratogenicity information for generating alerts

In Table 5, we present the agreement between the categories from FDA, FASS and ADEC. More specifically we show the various combinations of categories across sources, along with the number of prescriptions for the drugs in these categories. On examination, the agreement among the sources is limited.

The number of potential alerts generated based on FDA, FASS, ADEC is 305, 337 and 1438, respectively. Based on the mechanism of action, 8880 alerts would be generated. The results for each drug are presented in Table 6 and Table 8.

FDA	FASS	ADEC	Frequency	Example
C	B3	D	1027	FLUCONAZOLE
X	D	X	162	MISOPROSTOL
D	D	D	118	LISINOPRIL
C	D	D	56	CARBAMAZEPINE
X	B3	D	23	SIMVASTATIN
C	n.a.	D	18	OLMESARTAN MEDOXOMIL
C	C	D	18	NICOTINE
n.a.	n.a.	D	12	PROGESTERONE
D	B3	D	2	LETROZOLE
X	D	D	1	RIBAVIRIN
n.a.	D	D	1	PHENYTOIN

Table 5. Comparison of categories of teratogenic drugs according to FDA, FASS and ADEC (n.a. = non available, categories defined in [11])

Generic Name	ATC5	FDA	FASS	ADEC	Frequency
FLUCONAZOLE	J02AC01	**C**	**B3**	**D**	936
MISOPROSTOL	A02BB01	**X**	**D**	**X**	161
LAMOTRIGINE	N03AX09	**C**	**B3**	**D**	91
LISINOPRIL	C09AA03	**D**	**D**	**D**	77
CARBAMAZEPINE	N03AF01	**C**	**D**	**D**	33
SIMVASTATIN	C10AA01	**X**	**B3**	**D**	23
OXCARBAZEPINE	N03AF02	**C**	**D**	**D**	21
AZATHIOPRINE	L04AX01	**D**	**D**	**D**	18
NICOTINE	N07BA01	**C**	**C**	**D**	18
OLMESARTAN MEDOXOMIL	C09CA08	**C**	**n.a.**	**D**	16
PROGESTERONE	G03DA04	**n.a.**	**n.a.**	**D**	11
VALSARTAN	C09CA03	**D**	**D**	**D**	8
PHENOBARBITAL	N03AA02	**D**	**D**	**D**	5
RAMIPRIL	C09AA05	**D**	**D**	**D**	4
CAPTOPRIL	C09AA01	**D**	**D**	**D**	3
MERCAPTOPURINE	L01BB02	**D**	**D**	**D**	3
ALBENDAZOLE	P02CA03	**C**	**n.a.**	**D**	2
IRBESARTAN	C09CA04	**C**	**D**	**D**	2
LETROZOLE	L02BG04	**D**	**B3**	**D**	2
					TOTAL (ALL) = 1437

Table 6. Frequency of the top 20 potential alerts in a CDS based on the FDA category X or D, the FASS category D and the ADEC category X or D of a drug (from [11])

Generic name	ATC5 code	Mecanism of teratogenicity	Frequency
OLMESARTAN MEDOXOMIL	C09CA08	ACE inhibitors/AT II receptor antagonists	16
CAPTOPRIL	C09AA01	ACE inhibitors/AT II receptor antagonists	3
IRBESARTAN	C09CA04	ACE inhibitors/AT II receptor antagonists	2
TOPIRAMATE	N03AX11	Carbonic anhydrase inhibition	32
ACETAZOLAMIDE	S01EC01	Carbonic anhydrase inhibition	12
CELECOXIB	M01AH01	COX inhibitors	19
NABUMETONE	M01AX01	COX inhibitors	7
PIROXICAM	M01AC01	COX inhibitors	1
ESTRADIOL	G03CA03	Endocrine disruption	59
PROGESTERONE	G03DA04	Endocrine disruption	11
UROFOLLITROPIN	G03GA04	Endocrine disruption	2
LAMOTRIGINE	N03AX09	Folate antagonism	91
CARBAMAZEPINE	N03AF01	Folate antagonism	33
CLONAZEPAM	N03AE01	GABA receptor antagonists	126
LORAZEPAM	N05BA06	GABA receptor antagonists	77
BACLOFEN	M03BX01	GABA receptor antagonists	13
KETOCONAZOLE	J02AB02	Neural crest cell disruption	3
FERROUS SULFATE	B03AA07	Oxidative stress	1115
NIFEDIPINE	C08CA05	Oxidative stress	856
METRONIDAZOLE	P01AB01	Oxidative stress	727
ALPRAZOLAM	N05BA12	Oxidative stress	240
DIAZEPAM	N05BA01	Oxidative stress	84
ACETAMINOPHEN	N02BE01	Oxidative stress	64
ZIDOVUDINE	J05AF01	Oxidative stress	11
FERROUS GLUCONATE	B03AA03	Oxidative stress	5
PERPHENAZINE	N05AB03	Oxidative stress	4
NITROFURANTOIN	J01XE01	Oxidative stress	2
FERROUS FUMARATE	B03AA02	Oxidative stress	2
ISONIAZID	J04AC01	Oxidative stress	1
ONDANSETRON	A04AA01	Serotonin signalling disturbance	919
ARIPIPRAZOLE	N05AX12	Serotonin signalling disturbance	57
MIRTAZAPINE	N06AX11	Serotonin signalling disturbance	13
OLANZAPINE	N05AH03	Serotonin signalling disturbance	12
CABERGOLINE	G02CB03	Serotonin signalling disturbance	9
RISPERIDONE	N05AX08	Serotonin signalling disturbance	7
PINDOLOL	C07AA03	Serotonin signalling disturbance	6
ZOLMITRIPTAN	N02CC03	Serotonin signalling disturbance	5
GRANISETRON	A04AA02	Serotonin signalling disturbance	1
SUMATRIPTAN	N02CC01	Serotonin signalling disturbance	1

Table 7 (part 1/2). Frequency of potential alerts in a CDS based on mechanism of action (from [7])

IBUPROFEN	M01AE01	Vascular disruption	3536
NAPROXEN	M01AE02	Vascular disruption	166
MISOPROSTOL	A02BB01	Vascular disruption	161
HYDROCHLOROTHIAZIDE	C03AA03	Vascular disruption	103
LISINOPRIL	C09AA03	Vascular disruption	77
FUROSEMIDE	C03CA01	Vascular disruption	53
EPINEPHRINE	C01CA24	Vascular disruption	38
CARVEDILOL	C07AG02	Vascular disruption	25
ATENOLOL	C07AB03	Vascular disruption	19
SPIRONOLACTONE	C03DA01	Vascular disruption	13
ETODOLAC	M01AB08	Vascular disruption	12
MELOXICAM	M01AC06	Vascular disruption	11
VALSARTAN	C09CA03	Vascular disruption	8
BUMETANIDE	C03CA02	Vascular disruption	3
CLONIDINE	C02AC01	Vascular disruption	3
INDAPAMIDE	C03BA11	Vascular disruption	3
MEFENAMIC ACID	M01AG01	Vascular disruption	1
		TOTAL	**8880**

Table 8 (part 2/2). Frequency of potential alerts in a CDS based on mechanism of action (from [7])

Discussion

Findings

Identification of teratogenic drugs prescription. We performed an analysis of a large dataset of real prescription data, providing a broad view across all drugs. This is in contrast to most investigations, which focus on a specific drug or a small set thereof. We demonstrated that it was possible to associate teratogenicity categories from the main sources of teratogenicity information to prescription drugs from a clinical dataset, while restricting drugs to systemic drugs prescribed to pregnant women. By integrating NDC and ATC, drug terminologies, such as RxNorm, greatly facilitate the integration of drug information and the processing of medication datasets.

Clinical decision support. It is less clear, however, that the current sources of teratogenicity information can effectively support drug safety. The limited agreement among sources of teratogenicity information observed in our investigation corroborates the findings of other researchers. For example, disagreements in the biological effects and pregnancy risk category of the same ingredients stated in different structured product labels have been demonstrated by [13, 19]. In practice, the number of potential alerts generated by the different sources varies widely, from 305 to 1438 depending on the classification. Moreover, 8880 alerts would be generated for 9915 prescriptions based on the teratogenicity suggested by the mechanism of action of the drug, which is clearly inappropriate. The use of ADEC as a reference for teratogenicity information would result in generating the highest number of alerts compared to FDA and FASS, whose alerts are covered by ADEC. In contrast, the use of categories FDA "D" and "X" would result in generating fewer alerts, but with a higher precision.

Challenges

Missing information: Some of the information required for generating accurate alerts for drug safety in pregnancy is missing from the sources of teratogenicity information, namely dose and dose form information. Although this information is present in the clinical dataset, it cannot be leveraged for clinical decision support purposes, because it is not provided by the reference sources. This omission is surprising, since the teratogenic effect is by definition correlated with the quantity of drug to which the fetus is exposed. Similarly, the specific period of the pregnancy when exposure occurs is of critical importance for the teratogenic effect of a drug. Again, this information was absent from the sources of teratogenicity information. In our clinical dataset, to be inferred from a selection of diagnosis and procedure codes indicative of ongoing pregnancy in the past 90 days.

Excessive alerting: Some drugs listed as teratogenic by some sources are commonly prescribed and the reliability such recommendations is arguable. For example, "ferrous sulfate" is listed as a teratogenic drug based on its mechanism of action, "oxidative stress". This is not reflected in current medical practices, since iron prescription is commonly recommended for preventing anemia in pregnancy. In our reference paper [7], the oxidative stress mechanism is associated with the ATC class Iron preparations (B03A, level 3), of which the ATC drug "ferrous sulfate" is a member (B03AA07, level 5). Here, the association between a high-level drug class based on mechanism of action and a teratology category seems excessive and would result in unnecessary alerts. This phenomenon explains in part the high number of alerts generated based on the mechanism of action. Categorizing individual drugs rather than drug classes could help address this problem.

Along the same lines, a clear example of off-label use of drugs classified by the FDA as potentially harmful for the fetus but accepted in daily practice by the American College of Obstetrician Gynecologist (ACOG) is Magnesium Sulfate, classified by the FDA as category D, but accepted for use in lifesaving conditions, such as maternal seizures and fetal prematurity [20]. Other drugs that fall in the same category are Misoprostol, also a category D drug, but used for induction of labor orally and intracervically.

Limitations

Our prescription dataset records drugs dispensed to pregnant women, but we have no evaluation of drug adherence in our population. Nevertheless the compliance rates are generally high, and it has been suggested by others that prescription records provide a reliable source of data for the investigating drug teratogenicity [21].
Due to the absence of an explicit pregnancy status in our dataset, we had to infer the pregnancy status from a combination of diagnoses and procedure codes. As a result, we also imposed a strict time window of 90 days prior the date of the diagnosis or procedure as the period of reference for analyzing drug prescriptions. This restriction is not ideal, because it potentially results in excluding many prescriptions to pregnant women. On the other hand, it ensures that the prescriptions selected for analysis will correspond to pregnant women. As a consequence, the results obtained in this investigation cannot be generalized, since they may only reflect some of the prescriptions to pregnant women in our dataset.
Finally, because this investigation is based on the identifiers for prescription drugs, dietary supplements and other over-the-counter medications cannot be analyzed.

Conclusions

In this investigation, we used several sources of teratogenicity information to analyze drug prescriptions to pregnant women. Although interoperability between prescription drugs in our clinical dataset and drugs (or drug classes) in the reference sources was not an issue, we found little agreement among the sources of teratogenicity information. Moreover, while information such as dose and period of pregnancy plays an important role in the determination of teratogenicity, it was often absent from the reference sources. Therefore it is doubtful that the current sources of teratogenicity information can effectively support drug safety.

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